Paul Patterson: In Memoriam

Caltech neuroscientist Paul Patterson, whose career spanned developmental neurobiology, behavioral neuroscience, and neuroimmunology, passed away on June 25th at the age of 70 from an aggressive brain tumor. Patterson was a pioneer and an iconoclast who was not afraid to work outside of the scientific mainstream; consequently, he made a number of important and seminal contributions that opened up entire fields of research. As his colleague of almost 30 years at Caltech, I watched his scientific evolution and transformations with curiosity, some skepticism, and ultimately admiration.

Paul was a consummate scientist, in the sense that he was consumed with science. He was possessed of a restless imagination and a drive to find hard problems that others would be too timid or conservative to investigate. He pursued these challenges with vigor and passion to a degree that could strike some as bordering on the quixotic. Patterson's ability to forge his path, without regard for mainstream opinion, was a continuing theme throughout his career. In this respect he was the clear inheritor of the scientific temperament of his uncle, Clair Patterson, a professor of geochemistry at Caltech who pursued a lifelong crusade to demonstrate the danger posed to public health by lead poisoning, despite initial skepticism from his colleagues. Paul's friends, students, and close colleagues loved him, even as he occasionally exasperated them.

Patterson initially achieved widespread recognition for his seminal work on the phenotypic plasticity of neurotransmitter identity, which he carried out at Harvard Medical School's Department of Neurobiology in the mid-1970s. He pioneered methods for the primary culture of neonatal sympathetic neurons, one of the first types of isolated neuron to be grown in vitro. With his student Linda Chun, and working with Edwin Furshpan and David Potter, Patterson demonstrated that immature sympathetic neurons could, when cocultured with heart cells, switch their neurotransmitter phenotype from noradrenergic to cholinergic, a switch that was ultimately

demonstrated at the level of single cells (Patterson et al., 1978). This discovery was fundamental, as it falsified the assumption that each class of neuron was born with an immutable chemical profile. Importantly, this developmental plasticity was not a "tissue culture artifact": later work in collaboration with Harvard colleague Story C. Landis (currently Director of the NINDS) demonstrated that sympathetic neurons that innervate the sweat glands normally undergo such a switch in transmitter identity during development in vivo, in a manner dependent on target-derived factors (Landis and Keefe, 1983; reviewed in Francis and Landis, 1999). The concept of neurotransmitter phenotypic plasticity established by Patterson and colleagues has stood the test of time, its lasting significance reinforced by recent studies demonstrating such plasticity in the adult nervous system (Spitzer, 2012).

At the time, these findings had a broader impact on the field of neural crest development, as a prominent example of phenotypic specification by environmental signals, and they strongly influenced my own early research (some of which was performed in close collaboration with Paul [Anderson et al., 1991]). They also set the stage for Patterson's decade-long quest to identify the so-called cholinergic differentiation factor (CDF), the signal that controls this transmitter switch. Originally identified as a bio-activity detected in heart-cell-conditioned medium (Patterson and Chun, 1977), CDF was present in vanishingly small quantities. Following Patterson's move to Caltech in 1983, postdoc Keiko Fukada was able to carry out a heroic 100,000-fold purification of the factor.

With the protein in hand, sequence could be obtained (Yamamori et al., 1989). I remember walking into Paul's office as he was looking at the sequence of CDF. In a small voice, sounding slightly puzzled, he asked, (to the best I can recall) "Do you want to see something really strange?" Astonishingly, the sequence of CDF revealed that it was identical to leukemia inhibitory factor (LIF), a cytokine previously known for its role in the immune system. My impression was that Paul was surprised because he had expected that the CDF would be a novel protein. I don't know whether or not he found this disappointing, because Paul was not one to let his emotions show. In any case, this finding was a major step forward and opened the way to identifying the target-derived CDF in vivo. Further studies suggested that other ligands of the LIF coreceptors LIFRß and gp130 were as likely to play this role as LIF itself (reviewed in Francis and Landis, 1999; Glebova and Ginty, 2005). In fact, the in vivo target-derived CDF has yet to be identified.

At that point, Paul reached an important crossroads: Should he follow the biology of the neurotransmitter identity switch in vivo, identifying and following CDF even if it was not LIF? Or should he follow the biology of LIF and related cytokines, wherever it took him? He chose the latter, and over the next decade, he investigated the regulation and function of LIF in many contexts: neural stem cell self-renewal, the response to central and peripheral nerve injury, and inflammatory responses. This work opened up an entire field of study of the role of so-called "neuropoietic cytokines" in nervous system development, function, and disease (reviewed in Bauer et al., 2007) and marked the beginning of Patterson's transformation from a developmental neurobiologist to a neuroimmunologist.

It also led to an increasing focus on the neurobiology of brain disorders and translational research. Patterson's 23 years of service on the scientific advisory board of the Hereditary Disease

Foundation, for example, led him to pursue work on Huntington's Disease for over a decade. In this case, he applied his extensive experience in developing monoclonal antibodies to neuronal antigens to developing potential "intrabody" therapies for this incurable genetic disorder (Khoshnan et al., 2002).

However, it was Patterson's work on LIF that led him to become increasingly interested in understanding the effects of inflammation on brain development and neurodevelopmental disorders such as autism and schizophrenia. He was struck by epidemiologic studies indicating that the 1918 influenza epidemic was associated with a surge in the incidence of schizophrenia among children born during that period. Because respiratory infections are accompanied by immune responses that elevate inflammatory cytokines such as LIF, Patterson began to investigate the hypothesis that the maternal inflammatory response to infection was a major factor in the etiology of schizophrenia, due its deleterious effects on the development of the fetal brain.

He established a mouse model of maternal immune activation (MIA), first using human influenza virus and then double-stranded RNA poly (I:C) as a viral mimetic, and examined the effects of these treatments on the behavior of the offspring. In 2003, Patterson published a seminal paper demonstrating that activation of the maternal immune system during pregnancy caused significant behavioral changes in adult offspring (Shi et al., 2003). These changes included deficits in pre-pulse inhibition of the acoustic startle response, an assay thought to model cognitive deficits characteristic of autism and schizophrenia. The offspring also showed increased sensitivity to antipsychotic drugs such as chlorpromazine. This study led Patterson into a decade-long search to understand the relationship between MIA and neurodevelopmental disorders (Patterson, 2011b).

Patterson's research into the origins of autism and schizophrenia characteristically bucked the trend in the field. At a time when genomics was yielding increasing evidence supporting a genetic origin of these disorders, he continued to pursue the hypothesis that environmental influences on fetal brain development played a significant and perhaps crucial role. I remember a rather intense exchange following a talk by Patterson at a McKnight Foundation meeting in which a prominent geneticist bluntly questioned why anyone would try to argue for an environmental origin of autism when his and other data so strongly pointed to a genetic etiology. Paul responded that he was not denying a role for genetics, but rather was arguing that environmental factors were more important than the geneticists seemed to believe they were. The geneticist was unconvinced. This may (or may not) have been the first time that Paul directly faced such trenchant skepticism. Whatever the case, where others might have felt cowed or intimidated by such criticism, Paul stood his ground, and the debate ended in a standoff.

In light of Paul's work on phenotypic plasticity, his focus on environmental rather than genetic causes of autism and schizophrenia made perfect sense: it echoed his earlier emphasis on environmental rather than genetic control of neural development. He championed the view that in vertebrates, developing neurons and their precursors were plastic and that their ultimate phenotype was more strongly influenced by signals from their neighbors (the "American" plan) rather than by their lineage ancestry (the "European" plan), as in invertebrates. But at a time when genetic determinants of cell fate in vertebrates were receiving increasing attention, Patterson eschewed the cell nucleus and continued to focus on the role of cell-cell interactions and other environmental influences on cell fate.

I have wondered whether Paul's career-long emphasis on environmental rather than genetic mechanisms was a reflection of his scientific background, his style, or even his politics. His PhD training with Bill Lennarz at Johns Hopkins certainly focused him on the cell membrane. At the same time, I had the impression that, at some level, Paul preferred to pursue unfashionable approaches simply to avoid "doing what everyone else was doing." And then there was his inescapable 1960's persona: the pony tail, the left-wing politics, the penchant for Kennedy assassination conspiracy theories. Paul was at Harvard during the early 1970's, when leftist scientists such as Richard Lewontin and Jon Beckwith (founder of "Science for the People") were arguing that espousing genetic causes of behavioral disorders was inherently reactionary and oppressive (Beckwith, 2002) and challenging Harvard geneticist Bernard Davis and sociobiologist E.O. Wilson in vigorous public debates. Given that influential experience, I wondered whether his preference for "nurture" over "nature" might, even subconsciously, have been in part a reflection of his political worldview. But this may well be simply a projection onto Paul of my own experiences of that time.

While some viewed Paul's passionate focus on the MIA hypothesis as tending toward the fringes, the scientific mainstream began to take notice as his research began to provide evidence that elevated maternal levels of IL-6 during pregnancy could indeed produce defects in brain development and behavior in their offspring. He was invited to write a Perspective for *Science* (Patterson, 2007), and his work was even mentioned in an opinion piece in the *New York Times* (Velasquez-Manoff, 2012). Patterson's most recent effort to communicate his viewpoint more broadly was his publication of a book written for a lay audience, entitled "*Infectious Behavior: Brain-Immune Connections in Autism, Schizophrenia and Depression*" (Patterson, 2011a). The book is not simply an argument for the maternal inflammation hypothesis, but features a lively and entertaining discussion of the general problem of modeling disorders like autism and schizophrenia in mice, leavened with the fundamentals of developmental neuroscience. This engaging and accessible book highlights not only Paul's scholarship but also his scientific style and personality.

Given his tendency to publish his research in more specialized journals like *Brain, Behavior, and Immunity* and to eschew what British neuroscientist Jeremy Brockes once trenchantly described as "those well-known organs of spurious glamour," it is ironic that Patterson's last publication appeared in *Cell*. Sarkis Mazmanian, a young microbiologist at Caltech, engaged Paul and his graduate student Elaine Hsiao in a collaboration using the MIA model to test the idea that alterations in cellular

immune function might contribute to the etiology of neurodevelopmental disorders (Hsiao et al., 2012). In a follow-up study, the team demonstrated that offspring from maternally infected mice exhibited an altered gastrointestinal microbiome and leaky gut, associated with increased circulating levels of potentially neurotoxic metabolites. Strikingly, both the elevated levels of these metabolites and autism-like behavioral phenotypes in these offspring could be reversed by administration of the human commensal gut microbe *Bacteroides fragilis* (Hsiao et al., 2013).

The authors concluded that their results supported a "gut-microbiome-brain connection in a mouse model of ASD [Autism Spectrum Disorder], and identify a potential probiotic therapy for…human neurodevelopmental disorders." Not surprisingly, the idea that probiotic treatment could potentially cure autism provoked an explosion of interest in the popular media, promptly cited by 27 news outlets. While Patterson lived to see what was perhaps the greatest level of media and mainstream scientific attention to his work that he had ever experienced in his career, and felt optimistic and excited that he was finally on his way out of the wilderness, as it were, he died before being able to realize fully the fruits of this promising line of research.

Paul was as committed to education and the training of young researchers as he was to his science. He mentored scores of graduate students and postdoctoral fellows, many of whom have gone on to successful independent careers in research. His accomplished laboratory alumnae include former graduate student Allison Doupe, postdoctoral fellow Louis Reichardt, and many other notable trainees. Patterson also taught in the Cold Spring Harbor Neural Development course (together with Dale Purves and Corey Goodman) and several undergraduate courses at Caltech and directed the joint Caltech MD-PhD programs with UCLA and USC. His mentoring style combined a seriousness of purpose with a great sense of humor. He was demanding of his students and impatient with anything less than a total commitment to science (which he once likened to "running a Mom-and-Pop grocery store: a 16-hour-a-day occupation"); at the same time, he hosted countless parties at his home, with raucous satiric skits skewering departing laboratory alumnae. He insisted that guests prepare and bring exotic dishes, whose complicated recipes he assigned to lab members and friends too timid to demur, yet he reveled in sharing the joys of food and cooking with his extended scientific family.

Paul was driven, demanding, stubborn, inflexible, prickly, and occasionally exasperating. He was also warm, generous, helpful, inclusive, loyal, loving, and often hilarious. I remember looking down the hall each morning as I arrived at work, seeing Paul sitting alone in his spacious conference room quietly eating his breakfast cereal under the watchful eyes of his life-size Marilyn Monroe cutout, his lab a clear extension of his home. It still seems impossible to believe, as I walk down the same corridor and see a locked door at the end of the hall, that the conference room behind it is now empty, and the palpable energy and humor that it once radiated now gone.

Patterson is survived by his wife, Carolyn, and 14 year-old son, Paul Clair.

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